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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,975	11/19/2001	Olga Bandman	PF-0227-2 CIP	9661

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LEGAL DEPARTMENT
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EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/988,975	Applicant(s) BANDMAN ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) *21,23,26,28 and 37-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24,25,27 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Election filed July 23, 2003 (Paper No. 7) in response to the Office Action of June 6, 2003 is acknowledged and has been entered.

Claims 1-20 were cancelled.

Claims 21-40 were added.

Claims 21, 23, 26, 28, 37-40 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 22, 24-25, 27, 29-36 are currently under prosecution

Applicant's election with traverse of Group II, drawn to antibodies to SEQ ID NO:1 and methods of preparing said antibodies in Paper No. 7, page 9 is acknowledged. The traversal is on the ground(s) that the inventions are overlapping and that a search of Groups I, III-VII would not impose a serious burden on the examiner. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 6.

As to the question of burden of search, the inventions are classified differently, necessitating different searches in the literature. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. Applicants further point out that upon allowance of the claims of Group II, claims 23, 26-27, 31,

and 37-38 should be rejoined and considered in accordance with *In re Ochiai*. However, it is noted that Group II includes examination of claims 27 and 31, hence said claims cannot be subject to rejoinder. The remaining unexamined claims will be considered for rejoinder provided that they depend from or otherwise include all the limitations of the allowable product.
For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the current priority status of the present application. For example, USSN 09/478,957, filed 7 January 2000, is now USPN 6,350,448.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22, 24-25, 27, 29-36 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

The claims are broadly drawn to isolated antibodies (or compositions thereof) which specifically bind to a polypeptide of SEQ ID NO:1, including chimeric, single chain, Fab, $F(ab')_2$, and humanized versions of said antibodies. The claims are further drawn to methods of making polyclonal antibodies comprising immunizing an animal with SEQ ID NO:1 or methods of making monoclonal antibodies specific to SEQ ID NO:1. As set forth below, since the protein

comprising SEQ ID NO:1 lacks utility, antibodies and methods of making said antibodies specific to SEQ ID NO:1 also lack utility.

The disclosed utilities for antibodies that bind to the HUPAP protein comprising the amino acid sequence of SEQ ID NO:1, naturally-occurring amino acid sequences having at least 90% sequence identity to SEQ ID NO:1, fragments of SEQ ID NO:1 that bind to microtubules, and immunogenic fragments of SEQ ID NO:1, include the diagnosis, prognosis, treatment and evaluation of therapies for disorders of the prostate and gastrointestinal system. However, neither the specification nor any art of record teaches what the HUPAP protein is, how it functions, or a specific and well-established utility for any of the fragments claimed. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease. Additional disclosed utilities (page 3, line 1+) for anti-HUPAP antibodies include methods for treating cancers of the esophagus, stomach, small intestine, large intestine and colon; treatment of pancreatitis and ulcerative colitis. The asserted utility of the HUPAP protein is based on the assertion that HUPAP (SEQ ID NO:1) has chemical and structural homology with bovine enterokinase, human pancreatic kallikrein, and African rat renal kallikrein. The specification further proposes, based on sequence similarity to bovine enterokinase (page 8), that the HUPAP protein will function like a serine kinase (page 18, 2nd to last paragraph). However, evidence based on protein sequence homology does not alone permit extrapolation to an isolated amino acid's biological function or use thereof. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome

and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Thus, despite the 38% homology between HUPAP and bovine enterokinase, there is still an 62% difference and it cannot be predicted, based on the information in the specification, what affect this difference has on the function of the protein.

Additionally, Northern analysis revealed that HUPAP is expressed in ¾ patients with prostate cancer and was also expressed in spinal cord, colon tissue, and pancreatic islet cells

(page 18, last paragraph). However, those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Furthermore, Rama *et al.* (Biochem. J. Vol. 318, 1996, pages 333-341) teach that the glucocorticoid, betamethasone, increased mRNA expression of cholinephosphate cytidylyltransferase (CT) as determined by RT-PCR and Southern analysis, but did not alter the levels of the CT enzyme as assayed by Western blotting (abstract, and page 339, 2nd column, 2nd paragraph). Finally, it is well known that the basic molecular biology of eukaryotic gene transcription is tightly regulated. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Thus, the predictability of protein translation and its possible utility as a diagnostic or therapeutic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Furthermore, if a anti-HUPAP antibodies are to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many proteins, including HUPAP, are expressed in normal tissues and diseased tissues as so evidenced by the disclosure.

Therefore, one needs to know, e.g., that the claimed polypeptide is present only in diseased tissue to the exclusion of normal tissue. Thus, in the absence of any correlation between the HUPAP polypeptide with any known disease or disorder, any information obtained from various expression profiles only serves as the basis for further research on the observation itself.

Lastly, even if the polypeptide of SEQ ID NO:1 is a serine protease, neither the specification nor any art of record teaches what the polypeptide is, what it does, nor teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be immunogenic, or which fragments bind microtubules.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed antibodies and methods of making said antibodies. Thus, because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 24-25, 27, 29-36 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

If applicant were able to overcome the rejections under 35 USC 101 and USC 112 1st paragraph above, the following claims would still be rejected:

Claims 22, 24-25, 27, 29-36 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth an isolated antibody which specifically binds to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to antibodies which bind naturally occurring amino acid sequences having at least 90% sequence identity to the sequence of SEQ ID NO: 1, antibodies which bind a fragment of SEQ ID NO:1 wherein said fragment binds to microtubules, or antibodies which bind to an immunogenic fragment of SEQ ID NO:1, all of which read on antibodies that bind allelic variant polypeptides.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of allelic variant proteins encoded by allelic variant genes defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed fragments or amino acid sequences comprising 90% sequence identity to SEQ ID NO:1 and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed naturally occurring amino acid sequences.

Furthermore, although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the

claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for allelic variants is provided in the specification on page 5, where it is disclosed that an "allele" is an alternative form of a gene which may result from at least one mutation in the polynucleotide nucleic acid sequence. However, no disclosure, beyond the mere mention of allelic sequences is made in the specification. Further, there is no teaching of which fragments bind to microtubules or which fragments are immunogenically active.

Therefore only an isolated antibody which specifically binds to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, compositions thereof, and methods of making such antibodies, but not the full breadth of the claims, meets the written description provision of 35 USC 112, first paragraph.

Claims 22, 24-25, 27, 29-36 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said fragment binds to microtubules appears to have no clear support in the specification and the claims as originally filed. Hence, this is a new matter rejection. With respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims. See MPEP §714.02 and § 2163.06. If applicant should disagree with this rejection, applicant should submit evidence pointing to the serial number, page and line where support can be found for the disputed terminology.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
September 8, 2003